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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,439	08/19/2005	Thomas Hesterkamp	2335.0020001/SRL/KPQ	9959

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EXAMINER	
DUTT, ADITI	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,439	HESTERKAMP ET AL.	
	Examiner	Art Unit	
	Aditi Dutt	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *3-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 December 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

1. Applicant's election without traverse of Group I, represented by claims 1-2, 10,12 and 19, drawn to a method of diagnosing or prognosticating a neurodegenerative disease in a subject and Group A (transcription product of steroidogenic acute regulatory protein or fragment, variant or derivative thereof), in the reply filed on 22 January 2008 is acknowledged.

2. Claims 3-24, are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and to nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 22 January 2008.

3. Claims 1 and 2, drawn to a method of diagnosing or prognosticating a neurodegenerative disease in a subject, comprising determining the level or activity of a transcription product or fragments thereof, corresponding to a steroidogenic acute regulatory protein (Star) in a sample of the subject, are under consideration in the instant application.

Sequence Compliance

4. The disclosure is objected to because of the following informalities: This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37

CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825. The sequences in Figure 5 have nucleic acid sequences that are not associated with a relevant sequence identifier. Also, several sequences in the instant specification (pages 27, 25, for example) should be identified by SEQ ID NOs.

Appropriate correction is required.

Drawings

5. Figure 5 is objected to because it has a sequence that is not identified using a SEQ ID NO. Appropriate correction is required.

Specification

6. The disclosure is objected to because of the following informalities:

A) Arrangement of the Specification

Headings are missing between the various sections in the specification. Following guidelines should be followed:

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.

(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.

B) Brief Description of the drawings

The brief description of the drawing for figure 5 does not provide a SEQ ID NO. for the sequences in the figure.

Appropriate correction is required.

Claim Objections

7. Claim 1, is objected to because of the following informalities:

Claim 1 recites non-elected invention.

Appropriate correction is required.

Claim Rejections

Claim Rejections - 35 USC § 112-Second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1 and 2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention

9. The term "activity" in claim 1 is a relative term which renders the claim indefinite. The term "activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear what activities are encompassed by this phrase (i.e., ability of a transcription product to produce a biological effect, enzymatic activity, gene expression, gene activity, etc.).

10. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. Claim 1 fails to provide specific method steps to derive at the process for diagnosing or prognosticating a neurodegenerative disease.

11. Claim 1 is also rejected for reciting "a reference value". Does this refer to a "ratio" as stated in the example provided in the instant specification? Additionally it is also not clear as to how a skilled person can determine the presence of a disease by comparing with one reference value. It is not clear if the value represents a range of values.

35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1 and 2, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for diagnosing Alzheimer's disease comprising determining the level of a transcription product of the gene encoding Star in the frontal cortex relative to hippocampus region of postmortem brain tissue using RT-PCR, does not reasonably provide enablement for a method of diagnosis or prognosis of any neurodegenerative disease comprising the determination of the level or of any activity of the transcription product of Star or any fragments, derivatives or variants thereof, in any sample of the subject. The specification also does not enable the prognosticating or diagnosing of Alzheimer's disease by determining the level or activity of Star fragments, derivatives or variants thereof in any sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

13. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, include the nature of the invention, the state of the prior art, the predictability or lack

thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

14. The claims are drawn to a method of diagnosing or prognosticating a neurodegenerative disease in a subject, comprising determining the level or activity of a transcription product or fragments, variants or derivatives thereof, corresponding to a Star in a sample of the subject. The claims further recite that the disease is Alzheimer's Disease.

15. With respect to claim breadth, the standard under 35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification (see MPEP 2111 [R-1]), which states that claims must be given their broadest reasonable interpretation.

16. "During patent examination, the pending claims must be "given *>their< broadest reasonable interpretation consistent with the specification." *In re Hyatt,* 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the

claim, once issued, will be interpreted more broadly that is justified. *In re Prater*, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550-51 (CCPA 1969)".

17. As such, the broadest reasonable interpretation of the claimed method is for diagnosing or prognosticating any neurodegenerative disease in a subject, comprising determining the level or any activity of a transcription product or fragments, variants or derivatives thereof, corresponding to a Star in any sample of the subject.

18. The specification of the instant application teaches that Star is a synonymous gene on human chromosome 8p11.2 (page 5, para 2), encoding a 285 amino acid mitochondrial protein, wherein mutations of the gene have been associated with severe human diseases like lipoid congenital hyperplasia. The specification also teaches that Star binds cholesterol within the cytoplasm and shuttles between the mitochondrial and enclosed intermembrane space, and that the expression of Star is under the control of trophic hormones acting via the cAMP second messenger system. Furthermore, the instant specification using postmortem brain tissues from AD and control patients, demonstrates differential mRNA expression of Star gene in the frontal cortex relative to temporal cortex or the hippocampus of AD brain, but not in the age-matched control tissues by RT-PCR (page 5, para 1; Table 1 and 2). However, the instant specification as filed fails to provide any guidance for one skilled in the art on how to diagnose or prognosticate any neurodegenerative disease by determining the level or any

activity of any fragment or variant or derivative of a Star gene using any sample from the subject. Undue experimentation would be required to determine such. It is to be noted that the instant specification broadly defines activity as enzyme activity, levels of gene expression, biological effect, etc. (page 7).

19. Relevant literature teaches that Star can act as a cholesterol transfer protein and is important for the regulation of steroid biosynthesis (Stocco et al. Biochem Biophys Acta 1486: 184-197, 2000; abstract, Figures 1,2; Kallen et al. Mol Cell Endo 145: 39-45, 1998). Using fluorescence in situ hybridization, the art teaches that the Star locus was found in the human chromosomal region 8p11.2 (Sugawara et al. PNAS 92: 4778-4782, 1995; Figure 4). Sugawara et al. further demonstrate that Star mRNA was detected in the human ovary, testis and kidney, but not in the brain (Figure 1). However, the relevant art fails to provide any evidence or sound scientific reasoning that the limited information presented in the disclosure can directly be extrapolated to methods of diagnosis or prognosis of any neurodegenerative disease by determining gene expression levels of Star mRNA, or its fragments, variants or derivatives in any biological sample. There is no evidence from the instant specification or relevant art that all possible neurodegenerative diseases can be correlated to Star gene expression.

20. Furthermore, there is no evidence that the detection of Star

transcription products, if present in any body tissue or fluid, would reveal the presence of any neurodegenerative disease or indicate prognosis. The same question is also extended to detection of AD. It is not known whether the gene is present in any of the body fluids, if so whether the gene or its fragments or variants have any relevance with the claimed diseases, an answer that would require the skilled artisan to perform several trial and error tests resulting in undue experimentation. Additionally, though the data in the instant specification does not provide degrees of statistical significance (see Tables 1 and 2), it is noted that the average gene expression of frontal relative to temporal cortex has a greater deviation and overlapping of results from control versus AD, than the corresponding data for frontal relative to hippocampus ratio, the latter eliciting a higher fold differential expression in AD. This makes it even more evident that not only the selection of the tissue is important, but the regions within the brain tissue should be carefully considered for a predictable diagnosis. Furthermore, it is well accepted that different neurodegenerative disorders have different molecular origins, different etiology and pathology and involving different biochemical/physiological pathways. Thus, given the dearth of relevant information, the detection of Star transcripts and its innumerable fragments, variants and derivatives, to provide a diagnostic solution for all diseases, is akin to a fishing expedition for the skilled artisan.

21. The claimed diagnostic method based on the determination of fragments or variants or derivatives of a Star transcript is also highly unpredictable. The problem of predicting nucleic acid structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the DNA/RNA is extremely complex. While it is known that many nucleotide substitutions are generally possible in any given DNA or RNA the positions within the sequence where such substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the molecule's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of a Star gene encoding the Star protein of SEQ ID NO: 1 to enable one of ordinary skill in the art to determine without undue experimentation, the positions in the gene encoding SEQ ID NO: 1, which are tolerant to change (e.g. such as by substitutions or deletions of bases), and the nature and extent of changes that can be made in these positions. The art recognizes that function cannot be predicted from structure

alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

22. Since the molecular processes of pathogenesis of the various neurodegenerative diseases including AD are complex and yet to be fully uncovered, the success of diagnosis or prognosis would be unpredictable, thus the invention would entail undue experimentation by a skilled artisan. Therefore, one skilled in the art would not be able to predict from the instant specification that all possible neurodegenerative diseases would be diagnosed using the very broad method steps of the claimed invention. Undue experimentation would be required to determine such.

23. Due to the large quantity of experimentation necessary to diagnose any neurodegenerative disease using levels of transcription product of Star gene, the large quantity of experimentation to successfully diagnose AD or any other neurodegenerative disease by determining the expression levels of the infinite number of fragments, variants or derivatives of Star, measure any activity of Star or its fragments for diagnosis; the lack of direction/guidance presented in the specification regarding the same; the complex nature of the invention; the state of the prior art which establishes the unpredictability of the effects of modifying the structure and function of a nucleic acid or a protein;

and the breadth of the claims which fail to recite any structural or functional limitations - undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

35 USC § 112-Written description

24. Claims 1-2, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

25. The claims are drawn to a method of diagnosing or prognosticating a neurodegenerative disease in a subject, comprising determining the level or activity of a transcription product or fragments, variants or derivatives thereof, corresponding to a Star gene in a sample of the subject. The claims further recite that the disease is Alzheimer's Disease.

26. The specification of the instant application teaches that Star is a synonymous gene on human chromosome 8p11.2 (page 5, para 2), encoding a 285 amino acid mitochondrial protein, wherein mutations of the gene have been associated with severe human diseases like lipoid congenital hyperplasia. The specification also teaches that Star binds cholesterol within the cytoplasm and shuttles between the mitochondrial and enclosed

intermembrane space, and that the expression of Star is under the control of trophic hormones acting via the cAMP second messenger system. Furthermore, the instant specification using postmortem brain tissues from AD and control patients, demonstrates differential mRNA expression of Star gene in the frontal cortex relative to temporal cortex or the hippocampus of AD brain, but not in the age-matched control tissues by RT-PCR (page 5, para 1; Table 1 and 2). However, the brief description in the specification describing the diagnostic method with one example of the Star gene encoding the full length protein of SEQ ID NO: 1, one example of activity comprising the determination of gene expression level, one example of sample represented by frontal cortex, temporal cortex and the hippocampus of post mortem brain, and one neurodegenerative disease or Alzheimer's Disease, does not teach the functional or structural characteristics of Star or all its fragments, variants or derivatives in any tissue or body fluid sample, that can be used for diagnosing or prognosticating any neurodegenerative disease. The brief description in the specification demonstrating the determination of one Star gene encoding the full length protein of SEQ ID NO: 1, one activity, one sample, and one neurodegenerative disease, is not adequate written description of a diagnostic method comprising an entire genus of functionally equivalent fragments or variants or derivatives, an entire genus of samples, an entire genus of activities and an entire genus of neurodegenerative diseases. To provide adequate written description and evidence of

possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. However, in this case, the specification has not shown a relationship between the structure, function, or properties of the claimed genus of Star gene, and all possible fragments and variants thereof in the claimed diagnosis of any neurodegenerative disease or AD. The only factor present in the claims is the recitation of a diagnostic method comprising the determination of the level of Star transcription product for the detection of AD. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

27. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

28. With the exception of a diagnostic method comprising the determination of the level of Star transcription product for the detection of AD, the skilled artisan cannot envision the detailed chemical structure of all fragments, variants or derivatives in any sample, that could be used for diagnosing any neurodegenerative disease, by determining the level or activity of the Star molecules, and, therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or production. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The *antibody itself* is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

29. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

30. Therefore, only the diagnostic method for AD comprising the determination of gene expression of a Star gene encoding the full length Star protein in the frontal, temporal cortex tissues, or the hippocampus of the brain, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-*

Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

31. No claims are allowed.

32. The elected invention is free of the art.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.

34. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

35. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-

direct.uspto.gov/. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
30 September 2008

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649